COST-EFFECTIVENESS OF KETOSTERIL TREATMENT IN STAGE 3-4 CKD PATIENTS

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BACKGROUND

Chronic kidney disease (CKD) is a worldwide public health problem. There is a rising incidence and prevalence of kidney failure, poor outcome and high treatment costs. CKD is of growing importance in Hungary and a big public health problem affecting 10% of the Hungarian population and many of them have renal dysfunction as well. The essential aim of the treatment for predialysis patients is the reduction of the CKD progression. The absence of adequate predialysis therapy (diets, EPO, active vitamin D) decreases the quality of life and the chance of transplant and increases mortality.

The purpose of a Ketosteril (a ketoacid-aminoacid oral preparate) low-protein diet is to decrease the disease progression of predialysis patients (<60 ml/min) and to guarantee sufficient essential amino acid intake. Numerous publications confirmed that the supplementation of a low protein diet with Ketosteril reduces the progression of CKD compared to a diet without keto acid.

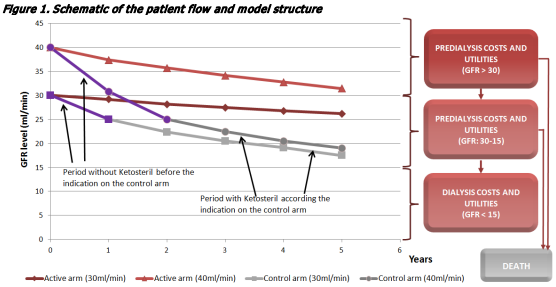
OBJECTIVES

Currently Ketosteril is reimbursed for patients with GFR<25 ml/min. Our aim was to evaluate the cost-effectiveness of Ketodiet extension (low/very low protein diet plus Ketosteril) of stage 3 (GFR 60-30 ml/min) of CKD versus starting in stage 4 (GFR 30-15 ml/min) of CKD. A simulation model has been developed to compare the relative costs and health-benefits of the two alternatives.

METHODS

Therapeutic effectiveness has been clarified by published Hungarian Ketosteril studies (n=171). GFR progression, of stage 3-4 CKD patients with and without Ketosteril treatment, was estimated with a statistical regression analysis. Regarding the available patient data two subgroups were defined on the basis of the starting GFR level to compare modeling arms. Next to the regression analysis 1000 hypothetical patient curves were generated using Bayesian posterior distribution to assure the validity of our preliminary hypothesis regarding the expected time to dialysis. Different disease stages were defined on the basis of the GFR level according to the international guidelines.

Figure 1. Schematic of the patient flow and model structure



The main driver of the model was GFR level and the dynamic of GFR-changes, which determined the actual stage of the patients that assigned the corresponding costs and utilities. The control arm corresponds with the existing practise of Ketosteril (GFR<25 ml/min), while the active arms were modeled the earlier start of keto therapy. Standard yearly population mortality risk was adjusted with disease specific mortality dependent from gender and age and used in every health stages. GFR<15 ml/min patients moved to dialysis stages, where probability of progression and mortality were equal in each arm.

Cost analysis of predialysis patients was performed on a multicenter (n=9) health care utilization data source with 80 Hungarian CKD patients. A questionnaire survey was undertaken with 4 Hungarian practitioner to determine the costs of dialysis, and common practice of the Ketosteril therapy. Unit costs (pharmaceutical, outpatient care services, labs, dialysis) were calculated on official list prices. All eligible costs items were cumulated during the end of study period or death..

Costs and health outcomes were registered and compute annually. The Hungarian yearly discount rate of 5% was used for both costs and outcomes. The time horizon was clarified on 30 years. Exchange rate was 300 HUF/€. Main outcome of the analysis was incremental cost of quality-adjusted life years (QALY). QALY values were clarified by published sources assigned to the CKD stages to assess the qualitative and quantitative impact of the two different Ketodiet approaches. Deterministic and probabilistic analyses were conducted from a payer perspective.

Table 1. Cost and utility inputs of the model

INPUT	VALUE	SOURCE
COSTS		
Direct medical cost with Ketosteril	2 780,15 €	Multicenter cost analysis
Direct medical cost without Ketosteril	836,57 €	Multicenter cost analysis
Dialysis cost	15 015,71 €	Questionnaire survey
UTILITIES		
GFR > 30	0,87	Nuijten et al
GFR 30-15	0,85	Nuijten et al
GFR < 15	0,5662	Nuijten et al

From 171 subjects 141 were enrolled into the analysis. Three methodological approaches were performed with different complexity to clarify the relevant GFR progression curves on patient data. Primary a simple regression model (Patient type analysis) was developed to specify 2 GFR progression curves for the active and control arms. On patient level analysis 141 patient specific curves were assigned, while on the simulation platform 38 400 different GFR progression were generated.

- **Analysis on patient type**: A cumulated curve was clarified for each arm on the basis of the Hungarian patient data. Different arms were defined by the initiation of Ketosteril therapy. In order to determine the equation for the GFR progression a mixed (calculating with fixed and random effect) regression were fitted. Progression of the different arms based on the fitted curve, which determined the time duration in the different health stages.
- **Analysis on patient level**: GFR progressions were assigned for every eligible individual. Costs and utilities were calculated on individual level as well. Final result for each arm was calculated on the average value of individual costs and utilities.
- **Simulation modeling**: basically 1000 new hypothetical patient curves (i.e. equation coefficients) were generated from the original patient data. Bayesian conditional probability was used to reflect limitation of the short term data regarding long term disease progression on the basis of published literature. Patient characteristics (classified by gender, age, starting GFR level) were taken into consideration, which had an influence to the estimated curve-equation (by coefficient or a constant). 192 patient profiles were defined by age (w 6 variables by decades), gender (w 2 variables) and starting GFR level (w 16 variables, between 25-40 ml/min). 100 random iterations were assigned to each profile (corresponds maximum 19 200 results for each arm).

RESULTS:

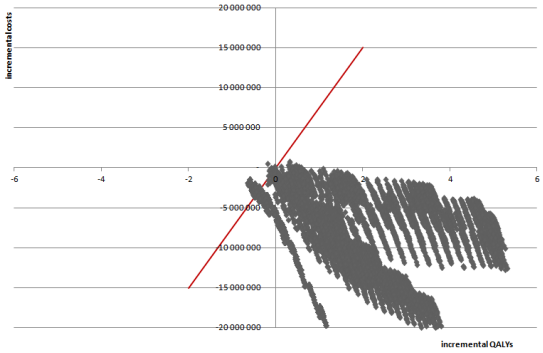
Deterministic modeling showed a cost advantage of 6 543,48 € at stage 3 of CKD patients versus stage 4. At stage 3 of CKD patients, Ketosteril treatment was found more effective (avg. difference: +0,71 QALY) than at stage 4. ICER was dominant in deterministic (-9 216,17 €/QALY) and also in probabilistic analysis (85,3% of cases) at stage 3 of CKD patients.

Table 2. Results of the deterministic modelling

	PATIENT TYPE ANALYSIS		PATIENT LEVEL ANALYSIS	
starting GFR level	30 ml/min	40 ml/min	30 ml/min	40 ml/min
IC Cost	-21 047,92 €	-16 245,50 €	-8 737,01 €	-6 543,48 €
IC QALY	-0,18	-0,34	0,75	0,71
ICER	**-116 932,91 €**	**-47 780,88 €**	**-11 649,35 €**	**-9 216,17 €**
	COST-EFFECTIVE	COST-EFFECTIVE	DOMINANT	DOMINANT

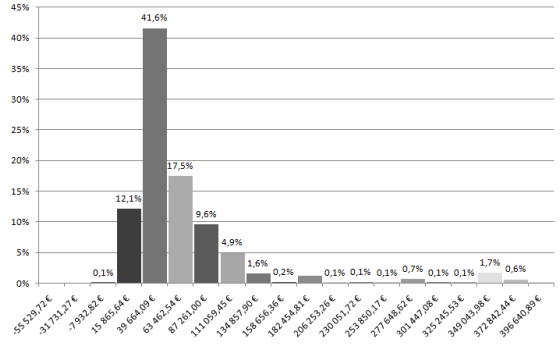
The majority of cases in the 19 200 iteration of the probabilistic analysis can be found in the dominant field. A result of the probabilistic analysis presented on a scatter plot figure. 85,3% of the cases CKD4 Ketosteril therapy resulted a dominant vs CKD3 Ketosteril therapy.

Figure 2. Scatter plot diagram of the probabilistic analysis



The following histogram includes those few (total 2 813 cases, 14,65%) subjects where cost-effectiveness threshold rate were relevant. The majority of cases is located within interval between -8 000-400 000 EUR/QALY.

Figure 3. Histogram of the probabilistic results



CONCLUSIONS

Our analysis presented three different methodologically approaches to evaluate the cost-effectiveness of Ketosteril treatment of stage 3 compare to stage 4 of CKD. The cost-utility analysis demonstrated that Ketosteril treatment in stage 3 CKD was a dominant strategy compared to stage 4 CKD in Hungary provided more advantageous in both healthcare costs and outcomes. Results were found robust, at each scenario most of the cases showed cost-effectiveness or dominancy.

Our results are limited due to patients' number and length of follow up in the primary data source. Statistical methods were applied to reduce biasing effect of these factors, but certainly these methods have limitation itself.

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